

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In Re Application of:

Shoenfeld *et al.*

Confirmation No.: 1174

Application Serial No. 09/806,400

Group Art Unit: 1644

Filing Date: March 30, 2001

Examiner: Ronald Schwadron

Title: COMPOSITIONS FOR THE PREVENTION AND/OR TREATMENT OF ATHEROSCLEROSIS

Mail Stop: Appeal Brief - Patents

Commissioner for Patents

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APPEAL BRIEF

Applicants file this Appeal Brief, in triplicate, pursuant to 37 C.F.R. § 41.37, in support of their Notice of Appeal, dated April 24, 2009, and filed concurrently with this Appeal Brief. This Appeal Brief is due on or before June 24, 2009. A check in the amount of \$270.00 is enclosed to cover the fee for filing a brief in support of an appeal required under 37 C.F.R. § 41.20(b)(2). Applicants do not believe any additional fees are due. However, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 50-0311, Reference 25619-501.

REAL PARTY IN INTEREST

The real party in interest is Vascular Biogenics, Ltd, the assignee of the application from all inventors.

RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences for this matter.

STATUS OF CLAIMS

Claims 1-27 are cancelled. Claim 28 is pending and is the subject of this appeal.

STATUS OF AMENDMENTS

No claim amendments were submitted after final rejection.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The sole independent claim on appeal is claim 28, which recites the following.

A method for treatment of atherosclerosis in a subject (claim 14 as originally filed) comprising:

- administering a therapeutically effective amount of an enteric coated tablet or granule composition (page 14, line 1 - page 15, line 4) comprising
- isolated human oxidized low density lipoprotein and a pharmaceutically acceptable carrier for oral administration (page 15, line 30 - page 16, line 11).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The rejection of claim 28 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. It is the Examiner's position that claim 28 is not enabled for treating humans and inducing oral tolerance.

ARGUMENT

Applicants appeal the Examiner's enablement rejection of claim 28 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

The Examiner states that the specification does not disclose how to use the claimed method to treat or prevent atherosclerosis in humans *in vivo* using an oral tolerance inducing amount of oxidized LDL. The Examiner further states that it is unpredictable whether human disease can be treated via inducing oral tolerance to a disease antigen. *See*, the instant Final Office Action at pages 4-6 and the Final Office Action mailed November 29, 2006 at pages 2-6. In support of the rejection, the Examiner recites *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) factors (5), (7), (3) and (2) against claim 28 at pages 4-6 of the instant Final Office Action and pages 3-4 of the Final Office Action mailed November 29, 2006.

State of the Prior Art (Wands Factor 5) and Predictability or Unpredictability of the Art (Wands Factor 7)

The Examiner states that regarding *Wands* factors (5) and (7), there is a high unpredictability in the art. Specifically, the Examiner cites Spack et al. *Expert Opin. On Invest. Drugs*, 6:1715-1727, 1997 ("Spack") and McKown et al., *Arthritis and Rheum.* 42:1204-1208, 1999 ("McKown") to show that it is unpredictable whether human disease can be treated via the induction of oral tolerance to a disease

antigen. *See*, the instant Final Office Action at pages 4-6 and the Final Office Action mailed November 29, 2006 at pages 4-5. The Examiner further cites George et al. *Cardiovasc Res.* 62(3):603-9, 2004 (“George”) to show that oral tolerance has proven successful in various immune models but yet efficacy in human disease is still pending. *See*, the instant Final Office Action at pages 4-5.

Applicants submit that pending claim 28 does not recite or require the induction of oral tolerance as stated by the Examiner. In fact, claim 28 is not directed to the induction of oral tolerance at all; rather, claim 28 is directed to a method of treating atherosclerosis by administering a therapeutically effective amount of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier for oral administration. As such, the Examiner’s arguments regarding the unpredictability of disease treatment via inducing oral tolerance to a disease antigen, including the discussion of McKown, Spack and George is misplaced and improper.

Applicants have previously argued in the December 7, 2005 Amendment and Response, August 31, 2006 Amendment and Response and the In-Person-Interview conducted on November 15, 2005 that the claims are directed to treating atherosclerosis and do not recite or require the induction of oral tolerance. However, the Examiner has stated that although the claims are not directed to a specific mechanism of action, the disclosure indicates that the claimed method works via oral tolerance and that the disclosure is sufficient to maintain the enablement rejection under 35 U.S.C. §112, first paragraph. *See*, the instant Final Office Action and the Final Office Action mailed November 29, 2006 at page 5 and the Office Action mailed March 3, 2006 at page 7.

The Examiner’s assertion is incorrect. It is well recognized under U.S. law, that it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works. *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989). It is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor’s theory or belief as to how the invention works a necessary element in the specification to satisfy the enablement requirement. *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983). A patent applicant need only teach how to achieve the claimed result, even if the theory of operation is not correctly explained or even understood. *In re Isaacs*, 347 F.2d 887, 892, 146 USPQ 193, 197 (C.C.P.A. 1965). Applicants submit that the instant application discloses a method of treating atherosclerosis by administering a therapeutically effective amount of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier for oral administration and thus satisfies the how-to-use requirement of 35 U.S.C. §112, first paragraph, irrespective of whether the claimed method works via oral tolerance or another unidentified mechanism.

The Presence or Absence of Working Examples (*Wands* Factor 3)

The Examiner states that regarding *Wands* factor (3), while the specification provides an example in a mouse model, there were copious amounts of mouse research that suggested that while oral tolerance could be used to treat multiple sclerosis and rheumatoid arthritis in such models, said diseases were not successfully treated in humans using oral tolerance. The Examiner again cites McKown, Spack and George to support this assertion. *See*, the instant Office Action at pages 4-6 and the Final Office Action mailed November 29, 2006 at pages 4-5.

As described *supra*, claim 28 is not directed to the induction of oral tolerance and is not directed to the treatment of multiple sclerosis or rheumatoid arthritis and the citation of Spack and McKown is not relevant to the currently recited invention. The instant invention and the additional data generated using the teachings of the specification and reported in the December 7, 2005 Harats § 1.132 Declaration, attached hereto in the Evidence Appendix, readily demonstrate to one of ordinary skill in the art how to make and use the present invention to treat atherosclerosis by oral administration of isolated human oxidized LDL.

Specifically, the instant specification and the additional data supplied in the December 7, 2005 Harats § 1.132 Declaration provides a working example that demonstrates the successful treatment of atherosclerosis in an LDL-receptor deficient mouse by oral administration of isolated human oxidized LDL. *See*, Specification at, e.g., page 15, lines 20-29; and page 18, line 18 to page 19, line 31. It is well recognized in the art that the LDL-receptor deficient mouse is the preferred animal model to evaluate the effects of pharmacologic agents on atherosclerosis. LDL-receptor deficient mice, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. *See*, August 31, 2006 Harats § 1.132 Declaration at ¶ 5-6 attached hereto in the Evidence Appendix.

Specifically, the use of animal models (*i.e.* murine models) to evaluate the effects of pharmacologic agents on atherosclerosis was well recognized in the art when the instant application was filed (*See*, e.g., Bocan, *Curr. Pharm. Des.* 4(1):37-52, 1998); and, the LDL-receptor deficient mouse was recognized in the art as a preferred model of atherosclerosis at the time of the instant application. (*See*, e.g., Ishibashi et al., *J Clin Invest.* 92:883-893, 1993; Lichtman et al., *Arterioscler. Thromb. Vasc. Biol.* 19(8):1938-44, 1999; Maron, R. et al., *FASEB J.* 14:A1199-(Abstr.), 2000). Moreover, mice having targeted inactivation of the apolipoprotein E (ApoE) gene and of the LDL-receptor gene, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 6.

To further support the rejection, the Examiner cites Wouters et al. *Clin. Chem. Lab. Med.* 43(5): 470-479, 2005 (“Wouters”) and states that Wouters, discloses that the LDL-receptor mouse displays cholesterol metabolic pathways not found in humans and as a consequence “this route can serve as a backup mechanism for lipoprotein clearance in LDL-receptor mice, yielding unforeseen side effects.” *See*, Final Office Action mailed November 29, 2006 at page 6. Although the LDL-receptor deficient mouse is not the optimal model for genetic human familial hypercholesterolemia, it is one of the most predictable models for human atherosclerosis and the likelihood of new molecules to work as anti-atherosclerosis drugs in humans is high (*See*, e.g., Babaei et al., *Cardiovasc Res.* 48(1):158-67, 2000; Burleigh et al., *Biochem Pharmacol.* 70(3):334-42, 2005; Chen et al., *Circulation.* 106(1):20-3, 2002; Collins et al., *Arterioscler Thromb Vasc Biol.* 21(3):365-71, 2001; Cyrus et al., *Circulation.* 107(4):521-3, 2003; Elhage et al., *Am J Pathol.* 167(1):267-74, 2005; Li et al., *J Clin Invest.* 106(4):523-31, 2000; Napoli et al., *Proc Natl Acad Sci U S A.* 99(19):12467-70, 2002). Human atherosclerotic plaques are infiltrated with lymphocytes and display an inflammatory phenotype that includes expression of pro-inflammatory cytokines. In this sense the LDL-receptor deficient mice have plaques similar to those of humans containing a significant number of lymphocytes (*See*, e.g., Roselaar et al., *Arterioscler Thromb Vasc Biol.* 16(8):1013-8, 1996). Moreover, therapeutic strategies that apply for atheroprotection in humans are similarly successful in LDL receptor deficient mice and may not be so in ApoE knockout mice (*See*, e.g., Wang et al., *Atherosclerosis.* 162(1): 23-31, 2002). These findings indicate that plaques developing in LDL receptor deficient mice may be more relevant to human atherosclerosis than other non-human models and thus, it is one of the most widely employed models for drug development in the field of atherosclerosis. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 6.

The Amount of Direction or Guidance Presented (*Wands* Factor 2)

The Examiner states that regarding *Wands* factor (2), there is no disclosure in the specification as to what doses would be used to induce the functional parameters recited in the claim which are related to properties of the oral tolerance induction mechanism. *See*, the instant Final Office Action and the Final Office Action mailed November 29, 2006 at pages 4-6.

Once again, as described in detail *supra*, claim 28 is not directed to the induction of oral tolerance but rather are directed to a method of treating atherosclerosis by oral administration of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier

Applicants have provided working examples that demonstrate the successful treatment of atherosclerosis by oral administration isolated human oxidized LDL in an LDL-receptor deficient mouse

and the LDL-receptor deficient mouse is the most art-recognized model of the biochemical and morphological effects of atherosclerosis. Further, the working examples provide a range of concentrations of the composition to treat atherosclerosis (*See, e.g.*, page 18, lines 27-29; page 19, lines 18-19). Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention, would be able to determine the corresponding doses useful in other species, including humans, without undue experimentation. The specification need not disclose what is well known in the art. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 7-8.

Argument Conclusion

As described *supra*, Applicants have provided several working examples, both in the specification and additional data confirming the results described in the specification, and demonstrated successful treatment of atherosclerosis by oral administration of isolated human oxidized LDL. Therefore, Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention would be able to readily determine how to make and use the present invention and respectfully request that the Board reverse the Examiner's rejection of claim 28 under 35 U.S.C. § 112, first paragraph.

CLAIMS APPENDIX

A claims appendix listing the pending claim on appeal is attached to the end of this paper.

EVIDENCE APPENDIX

An evidence appendix, including 37 C.F.R. §1.132 Declarations of Dror Harats and references submitted and entered into the record by the Examiner, is attached to the end of this paper.

RELATED PROCEEDINGS APPENDIX

A related proceedings appendix, indicating that there are no related proceedings, is attached to the end of this paper.

Respectfully submitted,

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APPENDIX
CLAIMS ON APPEAL

Claim 28 (Previously Presented) A method for treatment of atherosclerosis in a subject, comprising administering a therapeutically effective amount of an enteric coated tablet or granule composition comprising isolated human oxidized low density lipoprotein and a pharmaceutically acceptable carrier for oral administration.

EVIDENCE APPENDIX

This evidence appendix includes the Declaration of Dror Harats under 37 C.F.R. §1.132 filed with Applicants December 7, 2005 Amendment and Response. This §1.132 Declaration was entered into the record and considered by the Examiner in the Office Action mailed on March 3, 2006. The December 7, 2005 Declaration of Dror Harats under 37 C.F.R. §1.132 (including Figure 1) was resubmitted with Applicants November 25, 2008 Request for Continued Examination. The compete Declaration including Figure 1 was entered into the record and considered by the Examiner in the Final Office Action mailed December 3, 2008.

This evidence appendix also includes the Declaration of Dror Harats under 37 C.F.R. §1.132 filed with Applicants August 31, 2006 Amendment and Response. This §1.132 Declaration was entered into the record and considered by the Examiner in the Final Office Action mailed on November 29, 2006.

This evidence appendix also includes the following references submitted December 7, 2005 in a Supplemental Information Disclosure Statement and entered into the record by the Examiner in the non-final Office Action mailed March 3, 2006:

- Bocan, *Curr. Pharm. Des.* 4(1):37, 40-52, 1998;
- Ishibashi et al., *J Clin Invest.* 92:883-893, 1993;
- Lichtman et al., *Arterioscler. Thromb. Vasc. Biol.* 19(8):1938-44, 1999;
- Maron, R. et al., *FASEB J.* 14:A1199-(Abstr.), 2000;
- Babaei et al., *Cardiovasc Res.* 48(1):158-67, 2000;
- Burleigh et al., *Biochem Pharmacol.* 70(3):334-42, 2005;
- Chen et al., *Circulation.* 106(1):20-3, 2002;
- Collins et al., *Arterioscler Thromb Vasc Biol.* 21(3):365-71, 2001;
- Cyrus et al., *Circulation.* 107(4):521-3, 2003;
- Elhage et al., *Am J Pathol.* 167(1):267-74, 2005;
- Li et al., *J Clin Invest.* 106(4):523-31, 2000;
- Napoli et al., *Proc Natl Acad Sci U S A.* 99(19):12467-70, 2002;
- Roselaar et al., *Arterioscler Thromb Vasc Biol.* 16(8):1013-8, 1996; and
- Wang et al., *Atherosclerosis.* 162(1): 23-31, 2002.

These Declarations under §1.132 and these references are relied upon by Applicants in this appeal.

**APPENDIX
RELATED PROCEEDINGS**

None

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